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SYNTHESIS AND ANTICONVULSANT PROPERTIES OF A SERIES OF *N*-SUBSTITUTED 2-AZA-SPIRO[4.5]DECANE-1,3-DIONES AND 8-PHENYL-2-AZA-SPIRO[4.5]DECANE-1,3-DIONES

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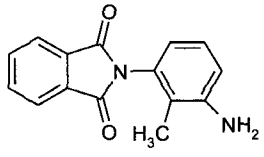
Abstract: A series of *N*-phenyl-2-aza-spiro[4.5]decane-1,3-diones [**III-VIII**], structurally related to the previously described *N*-phenyl-3-arylpyrrolidine-2,5-dione (11), was synthesized and tested for their anticonvulsant activity in the maximum electroshock seizure (MES) and metrazole seizure threshold (sc. MET) tests. The most potent of the series were *N*-(2-methylphenyl)-2-aza-spiro[4.5]decane-1,3-dione [**III**] and *N*-(3-methylphenyl)-2-aza-spiro [4.5]decane-1,3-dione [**IV**], which inhibited seizures in the MES and sc.MET tests. On the other hand, as a preliminary assay we synthesized and tested for the anticonvulsant activity a new *N*-substituted 8-phenyl-2-aza-spiro[4.5]decane-1,3-dione, containing either a benzyl or a cyclohexyl moiety [**IX-XII**] at the nitrogen atom. The obtained results showed that the presence and position of the methyl group in the aryl ring [**III, IV**], as well as an cyclohexane moiety [**XI, XII**] connected with the imide nitrogen atom, played the essential role for anticonvulsant activity.

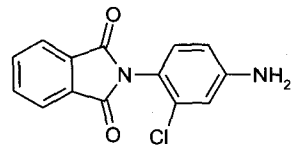
Keywords: anticonvulsant activity; *N*-phenyl substituted 2-aza-spiro[4.5]decane-1,3-diones; 8-phenyl-2-aza-spiro[4.5]decane-1,3-dione; spirosuccinimides

Previously, a great progress has been observed in research on new anticonvulsant drugs. The strategy of searching for new anticonvulsant drugs is going parallel by seeking the explanation of mechanism of action of the established drugs, as well as compounds being presently in the phase of clinical trials (1).

Anticonvulsant drugs are structurally different, which makes the structure-activity relationship studies difficult. In the past, several attempts were endeavored to propose a general pharmacophore for the different anticonvulsant drugs, and to find out some structural elements essential for the activity (2-4). In the search for the structure-activity relationships between the *N*-phenyl derivatives of phthalimide, Vamecq et al. (5) demonstrated that the presence of a phtalimide pharmacophore, the methyl or chloro substituents at 2-position of the *N*-phenyl ring, and the amine group situated in plane were essential for anticonvulsant activity. The structures of *N*-phenyl phtalimide derivatives with significant anti-MES activity are presented below:



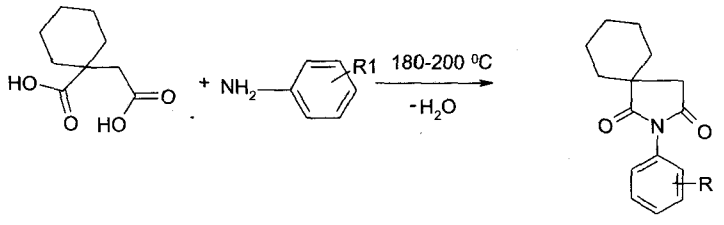
ED_{50} = 8.0 mg/kg



ED_{50} = 5.7 mg/kg

A study carried out by Scott et al. (6) on a group of spirosuccinimides showed the anticonvulsant activity for that type of compounds. Following investigations on the same group (7) and the crystallographic data of them (8) indicated an essential role of the cyclic system connected with the imide fragment through spiro carbon atom, regarding the influence of the compounds of this type on the anticonvulsant activity.

In the recent years, we have synthesized a great number of compounds with the anticonvulsant activity by changing the substituents at positions-1,3 of pyrrolidine-2,5-dione ring. Some of these were effective in anti-MES and sc.MET tests (9-12). Their synthesis was based on some earlier results of crystallographic studies (13). These results indicated that in the group of 1,3-substituted pyrrolidine-2,5-dione derivatives, the aromatic system increased liphophilicity, while the carbonyl groups with an adequate electrostatic potential, and selected substituents at the imide nitrogen atom are necessary for anticonvulsant activity.



I III-VIII

No.	III	IV	V	VI	VII	VIII
R	2-CH_3	3-CH_3	4-CH_3	2-CH_3, 5-Cl	3-Cl	4-Cl

Scheme 1.

Taking into account the above findings, in the present study we have synthesized a series of *N*-phenyl-2-aza-spiro[4.5]decane-1,3-dione [**III-VIII**] with the methyl or chloro substituents at the aromatic ring in respect to their anticonvulsant activity. On the other hand, we have undertaken studies concerned with the introduction of the phenyl ring into 4-position of the cyclohexane moiety to obtain a new class of derivatiyes with supplementary aromatic area, and to determine whether these modifications would increase the anticonvulsant activity. Therefore, as a preliminary study, we synthesized some new *N*-substituted 8-phenyl-2-aza-spiro[4.5]-decane-1,3-diones containing a benzyl or a cyclohexyl moiety [**IX-XII**] at the nitrogen atom, and we have tested them for anticonvulsant activity.

1-Carboxy-1-cyclohexane-acetic acid [**I**] and 1-carboxy-1-(4-phenylcyclohexane)-acetic acid [**II**] were obtained by the methods previously described (6,14). Thus obtained acids were used to synthesize *N*-substituted 2-aza-spiro[4.5]decane-2,3-diones [**III-VIII**] and 8-phenyl-2-aza-spiro[4.5]decane-1,3-diones [**IX-XII**] by heating them with the appropriate substituted phenyl-, benzyl- or cyclohexylamines. The synthesis of compounds **III-XII** are presented in Schemes 1 and 2.

The ^{1}H NMR spectra of the synthesized compounds were also studied.

The ^{1}H NMR spectra revealed a few characteristic chemical shifts of the investigated compounds. The chemical shifts of imide protons in the N-phenyl-2-aza-spiro[4.5]decane-1,3-dione derivatives **IV, V, VII, VIII** were displayed as singlets at δ 2.71 ppm. The signal of imide protons of the 2-methyl derivatives **III** and **VI** appeared as a doublet at ä 2.74-2.76 ppm, J = 4.4 Hz. The resonance signals of the methyl group appeared as a singlet at δ 2.12 ppm [**III**], δ 2.37 ppm [**IV**], δ 2.37 ppm [**V**] and δ 2.08 ppm [**VI**]. The chemical shifts of the cyclohexane ring in compounds **III-VIII** took the form of multiplets within the range of δ 1.32-1.96 ppm. The signals of aromatic protons for all the compounds of this series appeared as multiplets within the range of δ 7.04-7.45 ppm.

The ^{1}H NMR spectra of 8-phenyl-2-aza-spiro[4.5]decane-1,3-dione derivatives **IX-XII** showed a few characteristic chemical shifts. The imide protons were observed as a singlet at δ 2.53 ppm [**IX**], δ 2.51 ppm [**X**], δ 2.59 ppm [**XI**], and δ 2.56 ppm [**XII**]. The resonance signal of the methylene group, -CH_2-, appeared as a singlet at δ 4.64 ppm [**IX**] and at δ 4.59 ppm [**X**]. The ^{1}H NMR spectra of compounds **X**, **XII** showed protons of the -CH_3 group in the form of a singlet at δ 2.32 ppm [**X**] and a doublet at δ 1.04-1.07 ppm with the coupling constant J = 7.15 Hz [**XII**]. The signals of aromatic protons for all the compounds were seen as multiplets within the range of δ 7.09-7.37 ppm. The protons of cyclohexane rings were observed as multiplets at δ 1.19-2.30 ppm. The resonance signals of the protons (PhCH) of cyclohexane rings appeared as a doublet within the range of δ 2.48-2.51ppm, J = 3.6 Hz [**IX, X**] and a doublet of triplets δ 2.60-2.66 ppm, J = 3.85 Hz for compounds **XI**, and at δ 2.41-2.45 ppm for compound **XII**. The ^{1}H NMR spectra of **XI** and **XII** showed the proton (NCH) of cyclohexane rings as a doublet of triplets δ 3.94-4.01 ppm J = 3.85 Hz [**XI**] and δ 3.88-3.99 ppm J =3.85 Hz [**XII**]. The ^{1}H NMR spectral data strongly supported the chemical structures of compounds **III-XII**.

EXPERIMENTAL

Chemistry

Melting points (m.p.) were determined with an Electrothermal digital melting point apparatus, and

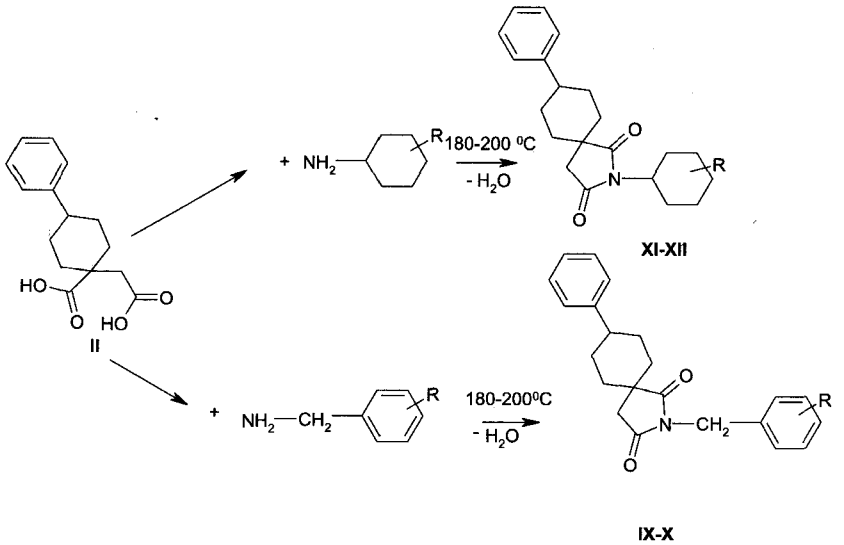
Table 1. Experimental data for compounds **III-XII**

Comp.	Formula MolecularMass	Yield [%] Mp.[°C]	Analyses (calcd/found)			R_f[a]
			%C	%H	%N	
III	$C_{16}H_{19}NO_2$ 257.3	68 93-95[c]	74.28 74.4	7.45 7.3	5.45 5.3	0.48 A 0.86 B
IV	$C_{16}H_{19}NO_2$ 257.3	62 110-112*	74.28 74.3	7.45 7.5	5.45 5.6	0.53 A 0.89 B
V	$C_{16}H_{19}NO_2$ 257.3	80 122-124	74.28 74.5	7.45 7.4	5.45 5.5	0.56 A 0.90 B
VI	$C_{16}H_{18}ClNO_2$ 291.8	78 205-207	65.81 65.7	6.21 6.1	4.80 4.7	0.44A 0.89 B
VII	$C_{15}H_{16}ClNO_2$ 277.8	82 144-150[c,b]	65.04 64.9	5.82 5.6	5.06 4.9	0.45 A 0.85 B
VIII	$C_{15}H_{16}ClNO_2$ 277.8	78 153-155[c,b]	65.04 65.2	5.82 5.9	5.06 5.1	0.43 A 0.83 B
IX	$C_{22}H_{23}NO_2$ 333.4	76 109-111	79.35 79.0	6.96 6.8	4.21 4.1	0.46 A 0.89 B
X	$C_{23}H_{25}NO_2$ 348.5	62 129-131	79.38 79.6	7.24 7.0	4.02 3.9	0.57 A 0.90 B
XI	$C_{21}H_{27}NO_2$ 325.5	68 175-177	77.61 77.5	8.37 8.5	4.31 4.5	0.76 A 0.90 B
XII	$C_{22}H_{29}NO_2$ 339.5	73 163-165	77.95 77.7	8.62 8.6	4.13 4.0	0.72A 0.92 B

[a] Solvent mixtures: A- ethyl acetate: n-hexane (3 : 7), B- chloroform : acetone (9 : 1)
[c] The Mp. values are in accord with ref. 15
[b] The Mp. values from ref. 15 are 137 °C [**VII**], 140° C [**VIII**]

Table 2. ^{1}H-NMR spectral data of compounds **III-XII**

Comp.	^{1}H NMR δ (ppm)/ $CDCl_3$
III	1.33-1.96 (10H, m, cyclohexane), 2.12 (3H, s, -CH_3) 2.74-2.76, (2H, d, imide, J = 4.4 Hz), 7.04-7.33 (4H, m, arom.).
IV	1.32-1.96 (10H, m, cyclohexane), 2.37 (3H, s, -CH_3), 2.71 (2H, s, imide), 7.04-7.37 (4H, m, aromat).
V	1.31-1.96 (10H, m, cyclohexane), 2.37 (3H, s, -CH_3), 2.71 (2H, s, imide), 7.12-7.27 (4H, m, arom.).
VI	1.32-1.98 (10H, m, cyclohexane), 2.08 (3H, s, CH_3), 2.74-2.75 (2H, d, imide, J = 4.6 Hz), 7.08-7.32 (3H, m, arom.).
VII	1.31-1.95 (10H, m, cyclohexane), 2.72 (2H, s, imide), 7.19-7.42 (4H, m, arom.).
VIII	1.32-1.95 (10H, m, cyclohexane), 2.72 (2H, s, imide), 7.23-7.45 (4H, m, arom.).
IX	1.51-2.30 (8H, m, cyclohexane), 2.49-2.51 (1H, d, cyclohexane J = 3.6 Hz), 2.53 (2H, s, imide), 4.64 (2H, s, -CH_2), 7.17-7.37 (10H, m, arom.).
X	1.51-2.28 (8H, m, cyclohexane), 2.32 (3H, s, -CH_3), 2.48-2.50 (1H, d, cyklohexane, J = 3.6 Hz), 2.51 (2H, s, imide), 4.59 (2H, s, -CH_2), 7.09-7.33 (9H, m, arom.).
XI	1.19-2.20 (18H, m, cyclohexane), 2.59 (2H,s, imide), 2.60-2.66 (1H, dt, cyclohexane, J = 3.85 Hz), 3.94-4.01 (1H, dt, cyclohexane, J = 3.85 Hz), 7.18-7.33 (5H, m, arom.)
XII	1.04-1.07 (3H, d, -CH_3, J = 7.15 Hz), 1.31-2.14 (16H, m, cyclohexane), 2.41-2.45 (1H, dt, cyclohexane, J = 3.85 Hz), 2.56 (2H, s, imide), 2.61-2.66 (1H, dt, cyclohexane, J = 3.85 Hz), 3.88-3.99 (1H, dt, cyclohexane, J = 3.85 Hz), 7.15-7.30 (5H, m, arom.).



No.	IX	X	XI	XII
R	4-H	4-CH_3	4-H	4-CH_3

Scheme 2.

are uncorrected. The chemical structures of the obtained compounds was confirmed by elemental and spectral analyses. ^{1}H NMR spectra (in $CDCl_3$) were recorded with a Varian Mercury spectrometer operating at 300 MHz. Chemical shifts were reported as parts per million (δ ppm) from $(CH_3)_4Si$ (TMS) as an internal standard. Signal multiplicities are represented by the following abbreviations: s (singlet), *d* (doublet), *dt* (double triplet), *m* (multiplet).

The elemental analyses for C, H, and N were found with an accuracy of ±0.4% of the theoretical values.

The purity of the compounds was checked by thin-layer chromatography (TLC) performed on Merck silica gel GF_{254} aluminium sheets, using the developing systems: A) ethyl acetate : n-hexane (3 : 7), B) chloroform : acetone (9 : 1). Spots were detected by their absorption under UV light, and by their visualization with 0.05 mol I_2 in 10 % HCl.

GENERAL PROCEDURE FOR THE PREPARATION OF *N*-PHENYL-2-AZA-SPIRO[4.5]DECANE-1,3-DIONES [**III-VIII**] AND *N*-BENZYL- OR *N*-CYCLOHEXYL-8-PHENYL-2-AZA-SPIRO-[4.5]DECANE-1,3-DIONE DERIVATIVES [**IX-XII**]

To the suspension of either 1-carboxy-1-cyclohexane-acetic acid [**I**] or 1-carboxy-1-(4-phenyl-cyclohexane)-acetic acid [**II**] (0.02 mole) in 20 mL of water, the appropriately substituted phenyl-, benzyl- or cyclohexylamine (0.02 mole) was gradually added. The mixture was heated in an oil bath, and water was simultaneously distilled off. After the complete removal of water, the temperature of the reaction mixture rose up to 190-200°C, and next the temperature was maintained for 1.5 h. After cooling, the precipitated crude products were recrystallized from 96% ethanol. Physicochemical data, yields, elemental analyses and R_f values are presented in Table 1. ^{1}H-NMR spectral data are shown in Table 2 .

It should be noted that compounds **III-V**, **VII** and **VIII** were previously reported by El-Talbany (15) (however, no ^{1}H NMR data are available), but none of them was tested for the anticonvulsant activity. Products **VI** and **IX-XII** are new ones.

Pharmacology

Preliminary pharmacological tests of the compounds **III-XII** have been provided by the Antiepileptic Drug Development (ADD) Program, Epilepsy Branch, Neurological Disorders Program, National Institute of the Neurological and Communicative Disorders and Stroke (NINCDS), Bethesda, by testing procedures which were reported earlier (16, 17). Phase I studies of the investigated compounds involved three testes: maximal electroshock (MES), subcutaneous metrazole (sc. MET), and rotorod test for neurological toxicity (TOX). Phase I involved i.p. administration of the compounds as suspension in 0.5% methylcellulose, and it was a

Table 3. Anticonvulsant screening project (ASP) phase I test in mice (**III-XII**)

Comp.	Dose mg/kg	MES[a]		sc.MET[b]		Tox[c]		ASP[d] class.
		0,5 h	4 h	0,5h	4 h	0,5 h	4 h	
	30	0/1	0/1	0/1	0/1	0/4	0/2	
III	100	3/3	0/3	0/1	0/1	0/8	0/4	1
	300	1/1	0/1	4/5	0/1	2/4	0/2	
	30	0/1	0/1	0/1	0/1	0/4	0/2	
IV	**100**	**0/3**	**0/3**	**3/5**	**0/1**	**1/8**	**0/4**	**1**
	300	**0/1**	**0/1**	**1/1**	**1/1**	**4/4[14]**	**0/2**	
	30	**0/1**	**0/1**	**0/1**	**0/1**	**0/4**	**0/2**	
V	**100**	**0/3**	**0/3**	**0/1**	**0/1**	**0/8**	**0/4**	**3**
	300	**0/1**	**0/1**	**0/1**	**0/1**	**1/4[14]**	**0/2**	
	10	**0/1**	**0/1**	**0/1**	**0/1**	**0/4**	**0/2**	
VI	**30**	**0/3**	**0/3**	**0/1**	**0/1**	**0/8**	**0/4**	**3**
	100	**0/1**	**0/1**	**0/1**	**0/1**	**0/4**	**0/2**	
	30	**0/1**	**0/1**	**0/1**	**0/1**	**0/4**	**0/2**	
VII	**100**	**0/3**	**0/3**	**0/1**	**0/1**	**0/8**	**0/4**	**2**
	300	**0/1**	**0/1**	**4/5**	**0/1**	**0/4**	**0/2**	
	30	**0/1**	**0/1**	**0/1**	**0/1**	**0/4**	**0/2**	
VIII	**100**	**0/3**	**0/3**	**0/1**	**0/1**	**5/8**	**0/4**	**3**
	300	-	-	-	-	**4/4[5]**	-	
	30	**0/1**	**0/1**	**0/1**	**0/1**	**0/4**	**0/2**	
IX	**100**	**0/3**	**0/3**	**0/1**	**0/1**	**0/8**	**0/4**	**3**
	300	**0/1**	**0/1**	**0/1**	**0/1**	**0/4**	**0/2**	
	30	**0/1**	**0/1**	**0/1**	**0/1**	**0/4**	**0/2**	
X	**100**	**0/3**	**0/3**	**0/1**	**0/1**	**0/8**	**0/4**	**2**
	300	0/1	0/1	2/5	0/1	1/4	0/2	
	30	0/1	0/1	0/1	0/1	0/4	0/2	
XI	**100**	**0/3**	**0/3**	**0/1**	**2/5**	**1/8**	**0/4**	**1**
	300	**0/1**	**0/1**	**2/5**	**0/1**	**1/4**	**1/2**	
	30	**0/1**	**0/1**	**0/1**	**0/1**	**0/4**	**0/2**	
XII	**100**	**0/3**	**0/3**	**0/1**	**2/5**	**5/8**	**0/4**	**1**
	300	**0/1**	**0/1**	**2/5**	**0/1**	**2/4**	**0/2**	

[a]Maximal electroshock test (number of animals protected/ number of animals tested); [b]Subcutaneous metrazole test; [c]Rotorod toxicity (number of animals exhibiting toxicity/ number of animals tested); [d]The classification are as follows: 1-anticonvulsant activity at doses 100mg/kg or less; 2-anticonvulsant activity at doses greater than 100mg/kg; 3-compound inactive at 300mg/kg.
Response comments: [5]Death following clonic seizure, [14]unable to grasp rotorod.

qualitative assay involving a small number of mice (1-4) at a dose levels of 30, 100, and 300 mg/kg. The compounds were classified as the following categories: anticonvulsant activity at 100 mg/kg or less (class 1), anticonvulsant activity at doses greater than 100 mg/kg (class 2), compounds inactive at 300 mg/kg (class 3).The results are shown in Tab]le 4.

RESULTS

N-phenyl-2-aza-spiro[4.5]decane-1,3-diones **III-VIII** exhibited some anticonvulsant properties in the phase I screening project or were inactive. In this series of compounds, *N*-(2-methylphenyl)-2-aza-spiro[4.5]decane-1,3-dione **III** was active at a dose of 100 mg/kg (3/3 animals protected at 0.5 h) and 300 mg/kg (1/1 animals protected at 0.5 h) in the MES test and at a dose of 300 mg/kg (4/5 animals protected at 0.5 h) in the sc. MET test. The 3-methyl analogue **IV** was also active at a dose of 100 mg/kg (3/5 animals protected at 0.5 h) and 300 mg/kg (1/1 animals protected at 0.5 and 4 h) in the sc. MET test. Substitution of the methyl group in 4-position of the phenyl ring of compound **V**, as well

as introduction of the chloro substituent into 5-position of compound **VI** made them inactive in both tests. 3-Chloro derivative **VII** was marginally active at a dose of 300 mg/kg (4/5 animals protected at 0.5 h) in the sc.MET. 4-Chloro analogue **VIII** was inactive, and at dose of 300 mg/kg it caused the death of animals following clonic seizures.

In the series of 8-phenyl-2-aza-spiro-[4.5]decane-1,3-diones, the introduction of a supplementary aromatic ring into 4-position of the cyclohexane fragments, and the conversion of the *N*-phenyl- to *N*-benzyl- substituents in **IX, X** did not improve their anticonvulsant activity. Compound **X** with the methyl group at 4-position of the phenyl ring showed a protective effect towards seizures at a dose of 300 mg/kg (2/5 animals protected at 0.5 h) in the sc. MET test. The *N*-cyclohexyl derivatives **XI** and **XII** were both active in the sc. MET test at a doses of 100 mg/kg (2/5 animals protected at 4 h) and 300 mg/kg (2/5 animals protected at 0.5 h).

In the neurological toxicity screening, the tested compounds **III, V, VI, VII, IX,** and **X** were nontoxic at a dose of 100 mg/kg. The mice were unable to grasp the rotorod after the administration of compounds **IV** (300 mg/kg at 0.5 h), and **V** (300 mg/kg at 0.5 h).

In conclusion, our study has shown that in the series of *N*-phenyl-2-aza-spiro[4.5]decane-1,3-dione derivatives, a significant role for the anticonvulsant activity depends on the kind and position of the substituents attached to the phenyl ring. The methyl group in 2- or 3-position of the phenyl ring increases the anticonvulsant activity [**III, IV**]. The presence of the chloro substituents makes the compounds either less potent [**VII**] or inactive [**VI, VII**]. On the other hand, among the new preliminary series of *N*-substituted 8-phenyl-2-aza-spiro[4.5]decane-1,3-dione derivatives, there are compounds with the anticonvulsant activity, namely *N*-cyclohexyl derivatives [**XI, XII**]. On the grounds of these findings we intend to synthesize a new series of *N*-cyclohexyl-8-phenyl-2-aza-spiro[4.5]decane-1,3-diones with various substituents at the cyclohexyl ring, as compounds with the potential anticonvulsant activity. The results of this study will be published soon.

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